mmoles) and N,N-dimethylaminopyridine (24 mg, 0.20 mmoles) are added. The reaction mixture is left at room temperature for 4 hours under stirring, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 1.4 g of the compound are obtained as an oil.

C) Synthesis of the 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(bromomethyl) phenyl ester (1.4 g, 3.18 mmoles) in acetonitrile (300 ml) silver nitrate (1 g, 6.36 mmoles) is added. The reaction mixture is heated at 50°C for 4 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.75 g of the expected compound are obtained as an oil.

D) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester

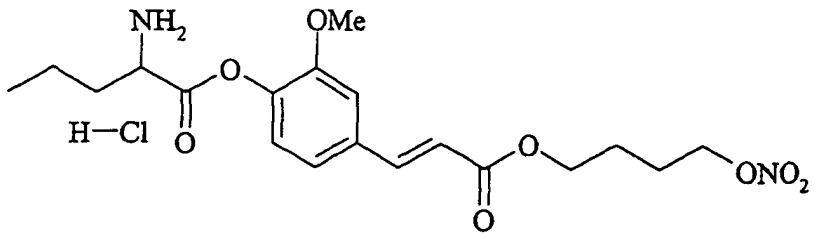
To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester (0.75 g, 1.8 mmoles) in ethyl acetate (5 ml), a solution of HCl 1N in ethyl acetate (18 ml) is added. The reaction mixture is left for 15 minutes at room temperature, then it is treated with n-hexane. The precipitate is filtered and dried under

vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 106°-108°C.

^{1}H-NMR (DMSO) ppm: 8.16 (3H, m); 7.52 (1H, t); 7.44 (1H,d); 7.34 (1H, s), 7.28 (1H, d); 5.65 (2H, s), 3.03 (2H, m); 2.86 (2H, s); 1.55 (10H, m).

EXAMPLE 4

Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylamino) pentanoic acid.

To a solution of 2-aminopentanoic acid (4 g, 34.14 mmoles) in dioxane (40ml) and water (75ml), triethylamine (9.5 ml, 68.29 mmoles) and di-tert-butyldicarbonate (8.94 g, 49.97 mmoles) are added. The reaction mixture is left at room temperature, under stirring for 17 hours. Afte having cooled the solution at 0°C it is brought to pH = 2 with HCl at 5%. One extracts with ethyl acetate, the joined organic phases are washed with water and dried with sodium sulphate.

The solvent is evaporated at reduced pressure to give the compound as an yellow oil which is used without further purification.

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmoles) in tetrahydrofuran (400 ml), tetrabromomethane (39.62 g, 119.47 mmoles) and triphenylphosphine (31.34 g, 119.47 mmoles) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The obtained crude compound is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C.

C) Synthesis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenolo (8 g, 24.3 mmoles) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmoles) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected compound are obtained as a yellow solid having m.p. = 65°-68°C.

C) Synthesis of the 2-(N-tert-butoxycarbonylamino) pentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid (0.5 g, 2.3 mmoles) in chloroform (12 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol (0.86 g, 2.76 mmoles), dicyclohexylcarbodiimide (0.52 g, 2.53 mmoles) and N,N-dimethylaminopyridine (0.03 g, 0.23 mmoles) are added. The reaction mixture is left at room

temperature for 1 hour under stirring, filtered and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 0.5 g of the expected compound are obtained as an oil. Yield 43%.

D) Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester (0.28 g, 0.548 mmoles) in ethyl acetate (7 ml), a solution of HCl in ethyl acetate (6.8 N, 0.700 ml) is added. The reaction mixture is left 3 hours at room temperature. The precipitate is filtered and dried under vacuum. 0.1 g of the expected compound are obtained as a white solid.

^{1}H-NMR (DMSO) ppm: 8.75 (3H, m); 7.62 (1H, d); 7.58 (1H, s); 7.3 (1H, d); 7.2 (1H, d); 6.72 (1H, d); 4.57 (2H, t), 4.26 (1H, t); 4.18 (2H, t); 3.82 (3H, s); 1.95 (2H, m); 1.75 (4H, m); 1.45 (2H, m) 0.98 (3H, m).

CLAIMS

1. Nitrooxyderivative compounds or salts thereof having the general formula (I):

$$A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2 \qquad (I)$$

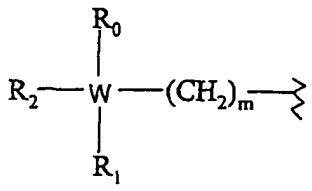
wherein:

c0 is an integer and is 0 or 1, preferably 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero;

A = $R\text{-}T_1\text{-}$, wherein

R is the radical of a precursor drug of formula II:



(II)

wherein:

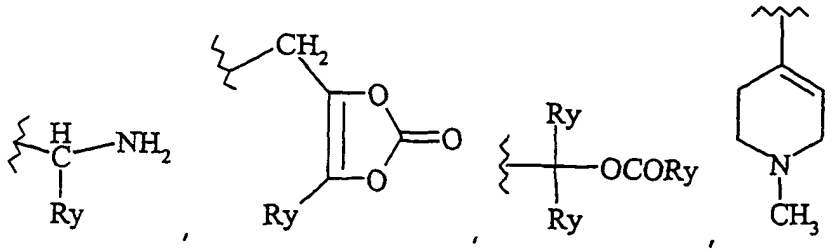
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

R_0 = H, $-(CH_2)_n\text{-}NHR_{1A}$, n being an integer from 0 to 2, wherein

R_{1A} = H, $-C(O)\text{-}R_{1H}$, $-C(O)O\text{-}R_{1H}$, wherein

R_{1H} is a linear or branched $C_1\text{-}C_{10}$ alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:



(II-B) (II-C) (II-D) (II-E)

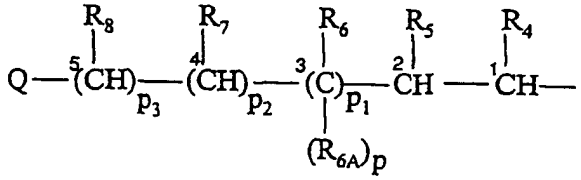
wherein Ry is hydrogen, a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group;

R_1 = H, when W = N, R_1 is the electronic doublet on the nitrogen atom (free valence);

R_2 is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- *mono- or di-hydroxy* substituted benzyl, preferably 3-4 di-hydroxy substituted;
- amidino group: $H_2N(C=NH)-$;

the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



(IIA)

wherein:

p, p_1, p_2 are integers, equal to or different from each other and are 0 or 1;

p_3 is an integer from 0 to 10;

R_4 is hydrogen, linear or branched C_1-C_6 alkyl, free valence;

R_5 can have the following meanings:

- linear or branched C_1-C_6 alkyl,
- C_3-C_6 cycloalkyl,
- free valence,
- OR_A, wherein R_A has the following meanings:
  - linear or branched C_1-C_6 alkyl optionally substituted with one or more halogen atoms, preferably F,
  - phenyl optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

R_6, R_{6A}, R_7, R_8, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type is present, between C_1 and C_2, R_4 and R_5 are free valences such as to form the double bond between C_1 and C_2; when the unsaturation is between C_3 and C_4, R_6 and R_7 are free valences such as to form the double bond between C_3 and C_4; when the unsaturation is between C_4 and C_5, R_7 and R_8 are free valences such as to form the double bond between C_4 and C_5;

Q is equal to H, OH, OR_B wherein R_B is benzyl, a linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups:

$-OCH_3$, $-CF_3$, nitro; or Q can have one of the following meanings:

- C_3-C_6 cycloalkyl;
- linear or branched C_1-C_6 alkyl;
- guanidine ($H_2NC(=NH)NH-$);
- thioguanidine ($H_2NC(=S)NH-$);

in formula (II) R_2 with R_1 and with W = C taken together form a C_4-C_{10}, preferably C_6, saturated or unsaturated, preferably saturated ring;

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1c}, R_{1c} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = $-T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above;

T_{BI}= $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

X_2, bivalent radical, is such that the corresponding precursor of B $-T_B-X_2-T_{BI}-$ wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with $-N(Z^I)(Z^{II})$, being:

Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible,

Z^I, Z^{II} equal or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of t, t', tx and txx;

the precursor compound of B as above defined is selected from the following classes of compounds:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetyl-penicillamine, cysteine, N-acetylcysteine, glutathione or esters thereof, preferably ethyl or isopropyl ester;
- hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic polyalcohols, selectd from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethylalcohol, coniferyl alcohol, allopurinol;
- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein

when b0 = c0 = 1: T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined,

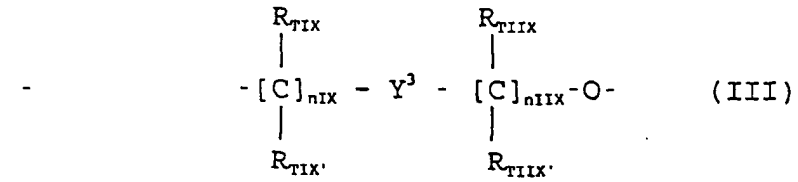
when b0 = 0 : T_c = (CO) when t = 0, T_c = X when t' = 0, X being as above defined,

when c0 = 0 : tx = 0, T_{BI} = X = –O–;

T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above;

Y has one of the following meanings:

Y_p :



(III)

wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

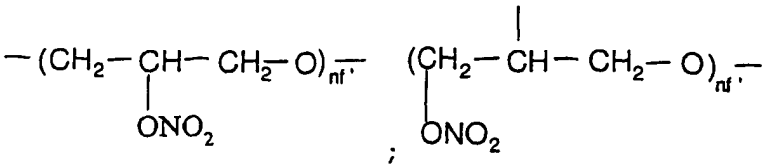
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing from 1 to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected from nitrogen, oxygen, sulphur;

or Y can be:

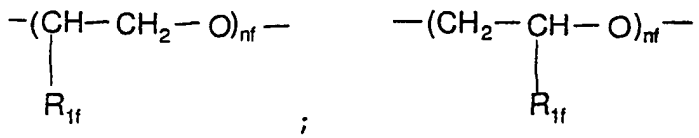
Y_0, selected from the following:

an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:

- 

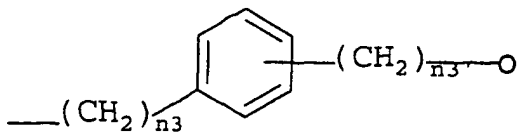
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- 

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 2 to 4;

Y_{AR}, selected from:

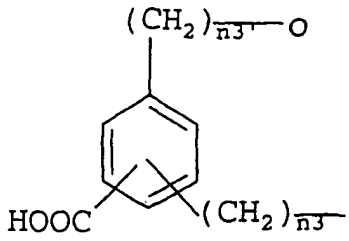
Y_{AR1}:



(V)

wherein n3 is an integer from 0 to 5 and n3' is an integer from 1 to 3; or

Y_{AR2}:



(VI)

wherein n3 and n3' have the above mentioned meaning.

2. Compounds according to claim 1, wherein:

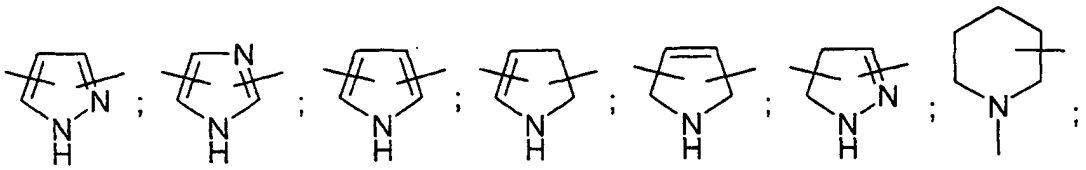
- when in formula (II) W = C, m = 1 and R_0 = $-(CH_2)_n-NH_2$ with n = 1, R_2 and R_1 with W as above form together the cyclohexane ring, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;
- when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;
- when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;
- when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the thioguanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;
- when in formula (II) W = C, m = 1 and R_0 = $-(CH_2)_n-NH_2$ with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the

free valence of A is saturated with OH, the precursor drug of R is known as pregabaline;

- when in formula (II) W = C and it has configuration (S), m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as (S)3-isobutylGABA;
- when in formula (II) W = C, m = 1 and R_0 = R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = NH and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;
- when in formula (II) W = C, m = 2 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 and R_5 are free valences and between C_1 and C_2 there is one ethylene unsaturation, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as vigabatrine;
- when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical 3-4 di-hydroxy substituted benzyl, T_1 = CO and the free valence of A is saturated with OH, the percursor drug of R is known as 2-amino,(3,4-dihydroxyphenyl)propanoic acid (dopa).

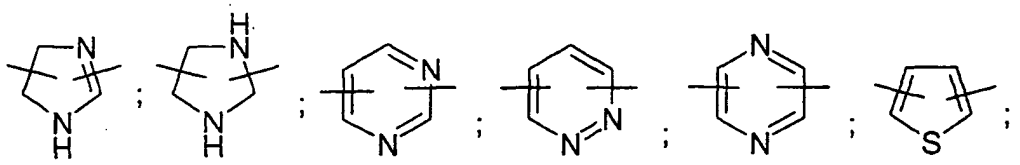
3. Compounds according to claims 1-2, wherein when in formula (I) b0 = 0, Y in the bivalent linking group C is selected between Y_P and Y_{AR} as above defined.

4. Compounds according to claim 3, wherein Y^3 is selected from the following bivalent radicals:

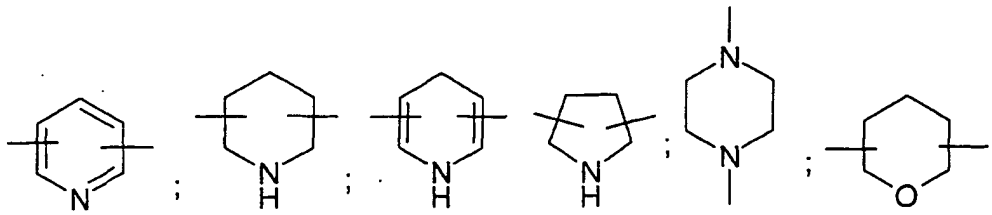


(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)

(Y19)



(Y7) (Y8) (Y9) (Y10) (Y11) (Y18)



(Y12) (Y13) (Y14) (Y15) (Y16) (Y17)

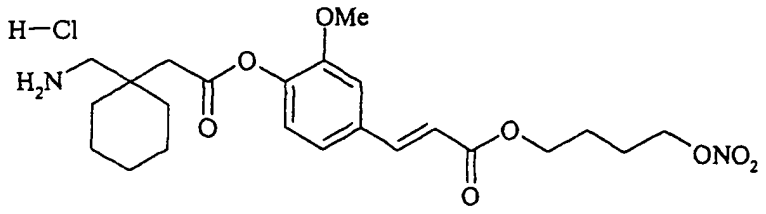
5. Compounds according to claim 4, wherein Y^3 is selected from (Y12), having the two free valences in the ortho position with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted; ; (Y19), wherein the free valence on the ring is found in para position to the nitrogen atom.

6. Compounds according to claims 1-5, wherein in formula (I) the precursors of B are the following: ferulic acid, N-

acetylcysteine, cysteine, caffeic acid, hydrocaffeic and gentisic acid.

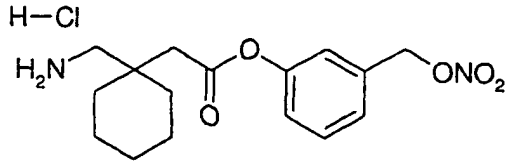
7. Compounds according to claims 1-6, wherein the precursor drugs are selected from gabapentine, norvaline, arginine, pregabaline, (S)3-isobutylGABA, agmatine.

8. Compounds according to claims 1-7, selected from the following: 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



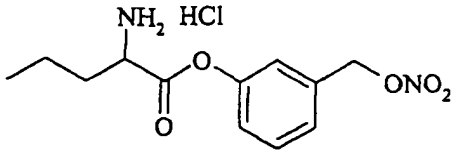
(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl) phenyl hydrochloride ester (XVI)



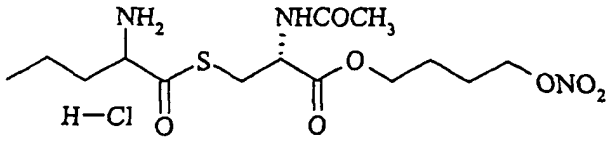
(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)



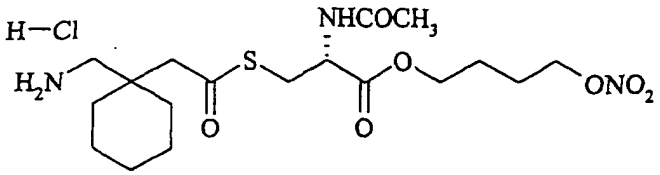
(XVII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino pentanoate hydrochloride (XVIII)



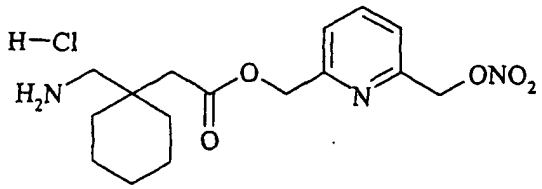
(XVIII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl) cyclohexanacetate hydrochloride (XIX)



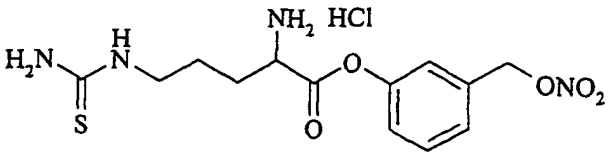
(XIX)

1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)



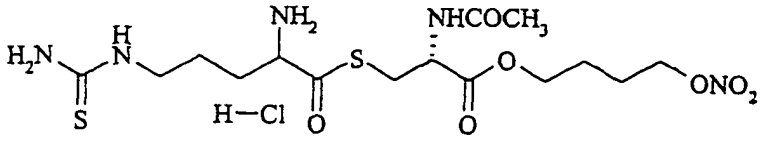
(XX)

alpha-amino-delta-thioureidopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXI)



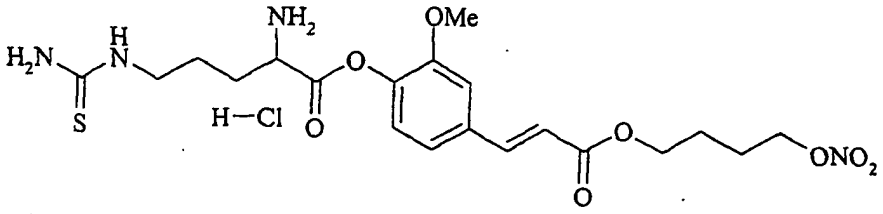
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hydrochloride (XXII)



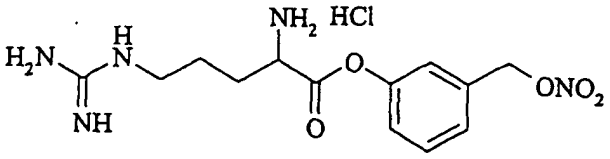
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



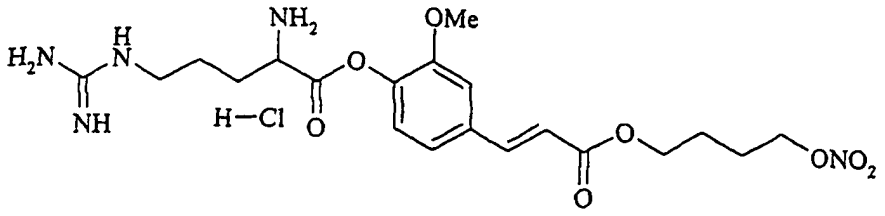
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



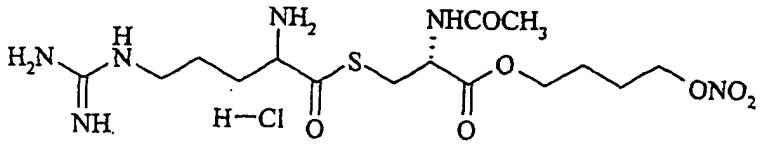
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



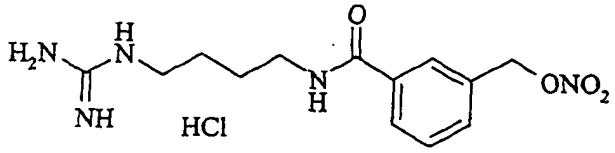
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



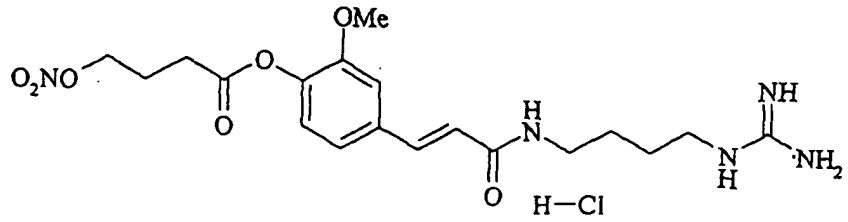
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



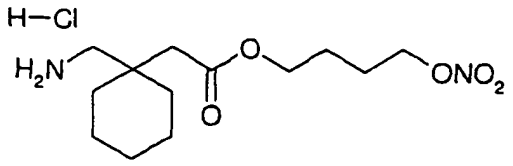
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)] phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy) butyl hydrochloride ester (XXIX)



(XXIX)

9. Compounds according to claims 1-8, as nitrate salts.
10. Compounds according to claims 1-9, in combination with NO donor compounds.
11. Compounds according to claim 10, wherein the NO donor compounds contain in the molecule radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen.
12. Pharmaceutical compositions for parenteral, oral and topical use comprising the compounds according to claims 1-11.
13. Compounds according to claims 1-12, for use as medicament.
14. Use of the compounds according to claims 1-13, for preparing drugs for epilepsy.

INTERNATIONAL SEARCH REPORT

al Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 C07C229/28 C07C229/08 C07C327/22 C07C335/08
C07D213/30 C07C279/14 C07C279/12 A61K31/195 A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199614 Derwent Publications Ltd., London, GB; Class B02, AN 1996-136303 XP002213051 & JP 08 027154 A (NIPPON KAYAKU KK), 30 January 1996 (1996-01-30) abstract	1,12-14
X	WO 00 54756 A (UNIV KINGSTON) 21 September 2000 (2000-09-21) page 3, line 27; claims 1,42	1,12-14
X	US 5 883 122 A (BENNETT BRIAN M ET AL) 16 March 1999 (1999-03-16) column 2, line 5; claims 1-13	1,12-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 2002	03. 12. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	CA 1 322 958 A (BOLGER GORDON T) 12 October 1993 (1993-10-12) page 1, line 18; claim 1	1,12-14
X	US 5 719 186 A (MUSSO DAVID LEE ET AL) 17 February 1998 (1998-02-17) column 3, line 63; claims 1,2	1,12-14
X	EP 0 372 998 A (BEECHAM GROUP PLC) 13 June 1990 (1990-06-13) abstract; claim 1	1,12-14
X	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) claim 1	1,12
X	WO 95 09831 A (NICOX LTD ;DEL SOLDATO PIERO (IT)) 13 April 1995 (1995-04-13) cited in the application abstract; claim 1	1,12
X	WO 97 16405 A (NICOX SA ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 9 May 1997 (1997-05-09) cited in the application claims 1-6	1,12
X	WO 01 12584 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 February 2001 (2001-02-22) cited in the application abstract; claims 1-13	1,12
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X	WO 00 61604 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) claims 1-12	1,12
P,X	WO 02 30867 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 18 April 2002 (2002-04-18) claim 1	1,12
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C.(Continuation) D CUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KAWASHIMA ET AL: "Synthesis and Pharmacological Evaluation of (Nitrooxy)alkyl Apovincaminates" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, 1993, pages 815-819, XP002210204 ISSN: 0022-2623 page 819, column 1; table 1	1,12
X	CIRINO G ET AL: "INHIBITION OF INDUCIBLE NITRIC OXIDE SYNTHASE EXPRESSION BY NOVEL NONSTEROIDAL ANTI-INFLAMMATORY DERIVATIVES WITH GASTROINTESTINAL SPARING PROPERTIES" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 117, no. 7, April 1996 (1996-04), pages 1421-1426, XP000938504 ISSN: 0007-1188 abstract	1,12
X	OGAWA T ET AL: "SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITIES OF NEW 1,4-DIHYDROPYRIDINE DERIVATIVES CONTAINING NITROOXYALKYLESTER MOIETIES AT THE 3- AND 5-POSITIONS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 6, no. 41, June 1993 (1993-06), pages 1049-1054, XP001093850 ISSN: 0009-2363 page 1054, column 1, paragraph 2; tables I-III	1,12
A	WO 00 44705 A (NICOX SA ;DEL SOLDATO PIERO (IT); GARUFI MICHELE (IT)) 3 August 2000 (2000-08-03) abstract; example 1	8
A	WO 98 42661 A (YISSUM RES DEV CO ;HAJ YEHIA ABDULLAH (IL)) 1 October 1998 (1998-10-01) claims 1-10	8
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A	WO 00 51988 A (NICOX SA ;DEL SOLDATO PIERO (IT); BENEDINI FRANCESCA (IT)) 8 September 2000 (2000-09-08) claims 1,9-13; examples 1-15	8

INTERNATIONAL SEARCH REPORT

national application No.
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B x I Observations wher certain claims were f und unsearchable (C ntinuation of it m 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-7,9-14
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-14 partially

   compounds having the following common structural feature: -(CH2)3-ONO2 useful for preparing drugs for epilepsy

2. Claims: 1-14 partially

   compounds having the following common structural feature: phenyl-CH2-ONO2 substituted in meta position, useful for preparing drugs for epilepsy

3. Claims: 1-14 partially

   compounds having the following common structural feature: 2-NO2-O-CH2-pyridyl which is substituted in the 6 position with the group -CH2-O-(CO)-, useful for preparing drugs for epilepsy

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7,9-14

Present claims 1-7, 9-14 relate to an extremely large number of possible compounds/uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 8 and of the examples 1-4.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty, only a few of them have been cited in the search report. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to the compounds of claim 8 and of the examples 1-4 as abovementioned.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/EP 02/06389

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